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Simple and One-Pot Protocol for Synthesis of Indene-spiro-oxindoles Involving Tandem Prins and Friedel–Crafts Reactions

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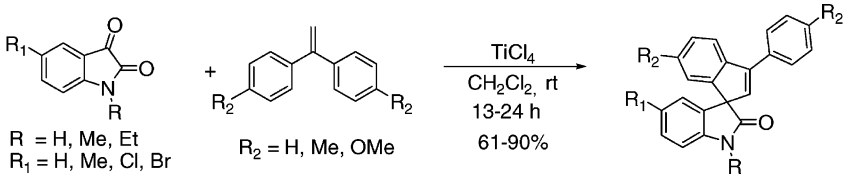
ABSTRACT



A simple and one-pot protocol for the synthesis of indene-spiro-oxindole derivatives via $TiCl_4$-mediated reaction between 1,1-diarylethylenes and isatin derivatives involving construction of two carbon–carbon bonds through tandem Prins and intramolecular Friedel–Crafts (PFC) reactions has been described. A plausible mechanism for this transformation is also presented.

Indene and spiro-indene derivatives[1] occupy a special place in organic and medicinal chemistry because these compounds are well-known h5-HT6 serotonin receptors, estrogen receptor modulators, antiproliferative agents, and oxytocin antagonists. The spiro-oxindole framework[2] represents yet another important structural organization present in a number of bioactive natural products such as coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine, alstonisine, surugatoxin, etc. With the view that the molecules containing both the indene and oxindole frameworks connected by an interesting spiro-bridge would be of biological interest and also aesthetically appealing and in continuation of our interest in the synthesis of heterocyclic molecules,[3] we herein report a facile reaction of 1,1-diarylethylenes with isatin derivatives under the influence of $TiCl_4$ to provide a novel one-pot protocol for the synthesis of 1*H*-indene-spiro-oxindole derivatives via the construction of two C−C bonds in an operationally simple process involving tandem Prins[4] and intramolecular Friedel−Crafts reactions[5] (PFC reaction sequence). We have been working for the last several years on various aspects of the Baylis−Hillman reaction,[3b−d] which is a popular, atom-economical, C−C bond forming reaction.[6] On the basis of our studies on the application of isatin derivatives as electrophiles in the Baylis−Hillman reaction[7]

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(1) (a) Kolanos, R.; Siripurapu, U.; Pullagurla, M.; Riaz, M.; Setola, V.; Roth, B. L.; Dukat, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1987−1991. (b) Watanabe, N.; Nakagava, H.; Ikeno, A.; Minato, H.; Kohayakawa, C.; Tsuji, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4317−4320. (c) Karaguni, I.-M.; Glusenkamp, K.-H.; Langerak, A.; Geisen, C.; Ullrich, V.; Winde, G.; Moroy, T.; Muller, O. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 709−713. (d) Evans, B. E.; Leighton, J. L.; Rittle, K. E.; Gilbert, K. F.; Lundell, G. F.; Gould, N. P.; Hobbs, D. W.; Dipardo, R. M.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.* **1992**, *35*, 3919−3927.

(2) (a) Chang, M.-Y.; Pai, C.-L.; Kung, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 8463−8465. (b) Baran, S. P.; Richter, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394−15396. (c) Hilton, S. T.; Ho, T. C. T.; Pljevaljcic, G.; Jones, K. *Org. Lett.* **2000**, *2*, 2639−2641. (d) Kosuge, T.; Tsuji, K.; Hirai, K.; Yamaguchi, K.; Okamoto, T.; Iitaka, Y. *Tetrahedron Lett.* **1981**, *22*, 3417−3420.

(3) (a) Basavaiah, D.; Rao, J. S.; Reddy, R. J.; Rao, A. J. *Chem. Commun.* **2005**, 2621−2623. (b) Basavaiah, D.; Satyanarayana, T. *Chem. Commun.* **2004**, 32−33. (c) Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604−605. (d) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, *3*, 3619−3622.

(4) For a leading review on the Prins reaction, see: Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672.

(5) For a leading reference on the Friedel−Crafts reaction, see: (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, pp 293−339.

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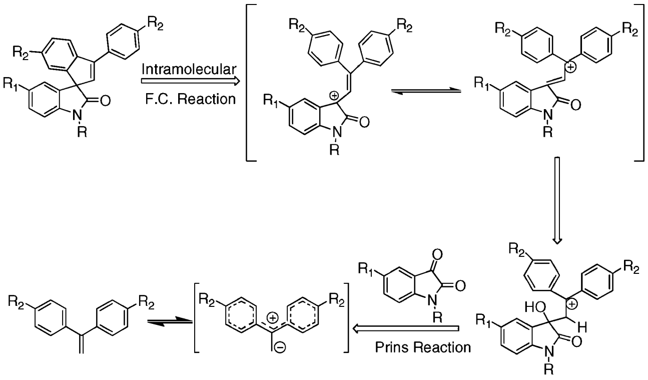
and on the basis of our recent work on the applications of isatin derivatives[3a] for the preparation of the spiro-oxindole [{1-acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane}-7-spiro-3′-(indolin-2′-one)] framework, we envisioned that the Prins reaction of 1,1-diarylethylenes with isatin derivatives followed by intramolecular Friedel−Crafts reaction would lead to the synthesis of 1*H*-indene-spiro-oxindoles (retro-synthetic strategy, Scheme 1).

Scheme 1. Retro-Synthetic Strategy: 1*H*-Indene-spiro-oxindoles



Accordingly, we first carried out the reaction between isatin (**1a**, 1 mmol) and 1,1-diphenylethylene (**2a**, 1 mmol) at room temperature under the influence of various acids (entries 1−6, Table 1). In this regard, the best results were obtained when a solution of isatin (**1a**, 1 mmol) and 1,1-diphenylethylene (**2a**, 1 mmol) in CH_2Cl_2 (3 mL) was treated with $TiCl_4$ (1 mmol) (addition at 0 °C) at room temperature for 13 h, thus providing the desired (3-phenyl-1*H*-indene)-1-spiro-3′-(indolin-2′-one) (**3**) in 90% isolated yield (Table 1, entry 5) after workup, followed by purification through silica gel column chromatography. The structure of this molecule was further confirmed by single-crystal X-ray data (see Figure 1).[8]

Table 1. Standardization: Reaction of Isatin (**1a**, 1 mmol) with Diphenylethylene (**2a**, 1 mmol) in CH_2Cl_2 (3 mL) at Room Temperature

entry	acid (mmol)	time (h)	% isolated yield of **3**
1	AcOH (1 mmol)	13	nil
2	*p*-TsOH (1 mmol)	13	nil
3	$MeSO_3H$ (1 mmol)	13	9
4	$SnCl_4$ (1 mmol)	13	nil
5	**$TiCl_4$ (1 mmol)**	**13**	**90**
6	$TiCl_4$ (0.5 mmol)	13	14

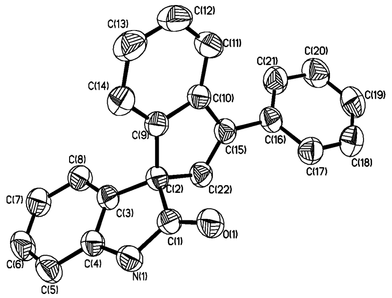
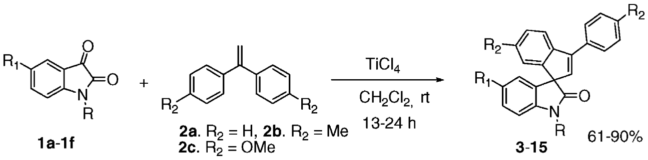


Figure 1. ORTEP diagram of compound **3**. Hydrogen atoms were omitted for clarity.

To understand the generality of this new Prins−Friedel−Crafts reaction, we have subjected various isatin derivatives (**1b**−**f**) to the reaction with 1,1-diarylethylenes (**2a**−**c**) under the influence of $TiCl_4$ to provide the resulting 1*H*-indene-spiro-oxindoles (**4**−**15**) in moderate to excellent yields (Table 2, entries 2−13). The structures of the molecules **5** and **14** were further confirmed by single-crystal X-ray data (for ORTEP diagrams, see Figures 2 and 3 in the Supporting Information).[8]

Table 2. Synthesis of 1*H*-Indene-spiro-oxindole Derivatives (**3**−**15**)[a]



entry	isatin	R	R_1	diarylethylene	time (h)	product[b]	yield (%)
1	**1a**	H	H	**2a**	13	**3**[c]	90
2	**1a**	H	H	**2b**	13	**4**	82
3	**1a**	H	H	**2c**	13	**5**[c]	69
4	**1b**	H	Cl	**2a**	18	**6**	77
5	**1b**	H	Cl	**2b**	18	**7**	80
6	**1b**	H	Cl	**2c**	18	**8**	88
7	**1c**	H	Me	**2a**	13	**9**	61
8	**1c**	H	Me	**2b**	13	**10**	79
9	**1c**	H	Me	**2c**	13	**11**	76
10	**1d**	H	Br	**2c**	18	**12**	64
11	**1e**	Me	H	**2c**	18	**13**	72
12	**1f**	Et	H	**2a**	24	**14**[c]	63
13	**1f**	Et	H	**2c**	18	**15**	71

[a] All reactions were carried out on a 1 mmol scale of isatins (**1a**−**f**) with 1 mmol of diarylethylenes (**2a**−**c**), under the influence of 1 mmol of $TiCl_4$ in CH_2Cl_2 at room temperature. [b] All compounds were fully characterized (see Supporting Information). [c] Compounds were further confirmed by single-crystal X-ray data (see Supporting Information).[8]

To understand the mechanistic pathway, we have quenched the reaction in the case of **1a** (1 mmol) with **2a** (1 mmol) in

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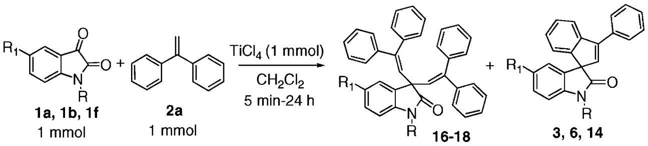
(6) For leading reviews on the Baylis−Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (c) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001−8062. (d) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670.

(7) Basavaiah, D.; Rao, A. J. *Tetrahedron Lett.* **2003**, *44*, 4365−4368.

(8) Structures were confirmed by single-crystal X-ray data. CCDC numbers for **3**, **5**, **14**, and **16** are 618512, 618513, 618514, and 618515, respectively.

the presence of $TiCl_4$ (1 mmol) with water after 5 min of stirring at 0 °C. Usual workup and purification through silica gel column chromatography provided the desired product, (3-phenyl-1*H*-indene)-1-spiro-3′-(indolin-2′-one) (**3**), in only 17% isolated yield and the bisadduct, 3,3-bis(2,2-diphenylvinyl)indolin-2-one **16**, in 45% isolated yield (Table 3, entry 1) (along with recovered isatin, **1a**). The structure of this molecule (**16**) was further established by single-crystal X-ray data (see Figure 2).[8]

Table 3. Control Reactions between Isatins and Diphenylethylene



entry	isatin	time	temp	product	yield[a] (%)	product	yield[b] (%)
1	**1a**	5 min	0 °C	**16**[c]	45	**3**	17
2	**1b**	5 min	0 °C	**17**	37	**6**	16
3	**1f**	24 h	rt	**18**	23	**14**	63

Isolated yields [a]based on alkenes and [b]based on isatins. [c]The structure of the molecule was further confirmed by single-crystal X-ray data (see Supporting Information).[8]

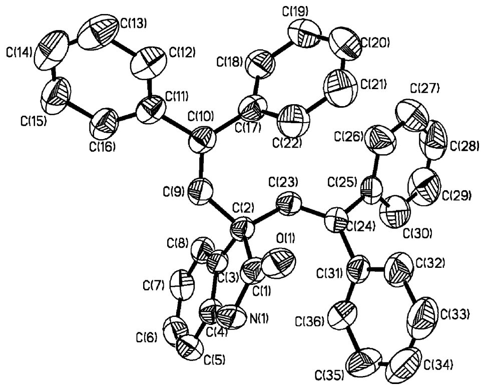
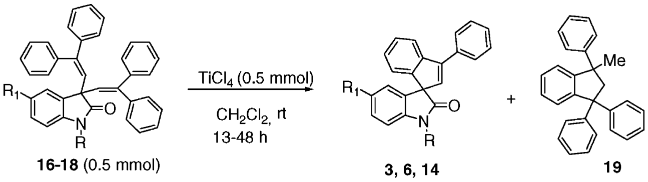


Figure 2. ORTEP diagram of compound **16**. Hydrogen atoms were omitted for clarity.

In similar reactions of **2a** with substrates **1b** and **1f**, we isolated the bisadducts **17** and **18** in 37% and 23% yields, respectively, and spiro-oxindoles **6** and **14** in 16% and 63% yields, respectively (Table 3, entries 2 and 3). From these reactions, it appears that the bisadduct might release 1 equiv of the alkene, thereby providing the desired spiro-oxindoles. To examine this aspect, we have treated the bisadducts **16**−**18** in CH_2Cl_2 with $TiCl_4$ (Table 4, entries 1−3) at room temperature. As expected in the case of **16** and **17**, the required spiro-oxindoles, **3** and **6**, were obtained in 85% and 88% isolated yields, respectively, whereas in the case of **18**, the required product **14** was isolated only in 36% yield (along with a substantial amount of the starting material **18**). In all three cases, in addition to the spiro-oxindoles, we have also isolated 3-methyl-1,1,3-triphenylindane **19** (Table 4) (see Supporting Information). It is worth mentioning here that the reaction of diarylethylenes with aldehydes in the presence of trimethylsilyl iodide providing the corresponding bisadducts, i.e., 1,1-bis(2,2-diarylvinyl)alkanes, and the transformation of diphenylethylene into 3-methyl-1,1,3-triphenylindane under the influence of $TiCl_4$−HCl and other acidic conditions are known in the literature.[9,10]

Table 4. Reaction of Bisadducts with $TiCl_4$[a]

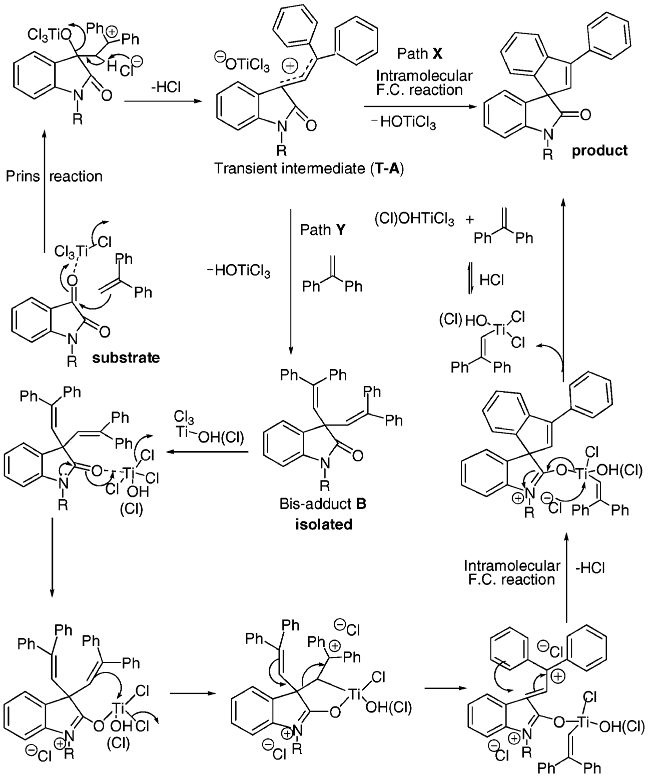


entry	bisadduct	time (h)	product	yield[b] (%)	product	yield[b] (%)
1	**16**	13	**3**	85	**19**	60
2	**17**	18	**6**	88	**19**	70
3	**18**	48	**14**	36	**19**	22

[a] All reactions were carried out on a 0.5 mmol scale. [b] For yields, see the Supporting Information.

These results, to some extent, might suggest a plausible mechanism (Scheme 2) which involves the reaction between

Scheme 2. Plausible Mechanism



1 equiv of isatin and 1 equiv of diarylethylene under the influence of $TiCl_4$ to provide the transient intermediate **T-A** which might then undergo intramolecular Friedel−Crafts reaction to generate the desired 1*H*-indene-spiro-oxindoles (path X). Alternatively, the **T-A** might also react with diarylethylene to give first bisadduct **B** which would then release 1 equiv of diarylethylene[11] to provide the desired 1*H*-indene-spiro-oxindole (path Y). Diarylethylene[11] in turn would again react with isatin to furnish the expected product, 1*H*-indene-spiro-oxindole.

In conclusion, we have developed a simple and one-pot $TiCl_4$-mediated synthesis of 1*H*-indene-spiro-oxindoles involving tandem Prins and Friedel−Crafts (PFC) reactions, using diarylethylenes and isatins as reaction partners.

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Supporting Information Available: Experimental procedures (with all spectral data), ^{1}H and ^{13}C NMR spectra of all compounds **3−19**, CIF files, and ORTEP diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Thomas, R. R.; Chebolu, V.; Sen, A. *J. Am. Chem. Soc.* **1986**, *108*, 4096−4103. (b) Evans, A. G.; Owen, E. D. *J. Chem. Soc.* **1959**, 4123−4125.

(11) It may be a diarylethylene-equivalent species containing titanium.